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Disease-a-Month

Medical Treatment of Cancer of the Breast and Prostate

HENRY M. LEMON

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Medical Treatment of Cancer of the Breast and Prostate

HENRY M. LEMON

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Henry M. Lemon

is Associate Professor of Medicine at Boston University School of Medicine and Consultant in Internal Medicine to the Boston Veterans Administration Out-Patient Clinic. Since 1948, he has administered the cancer teaching program at the School of Medicine, and served as Executive Secretary of the Massachusetts Memorial Hospitals Tumor Clinic. In 1949, he established the Hormone Research Laboratory at Boston University. Major cancer contributions have included cytodiagnostic methods for gastrointestinal cancer (1948–1949), introduction of the hamster cheek pouch method for transplantation of human tumors (with Dr. Brenton W. Lutz, 1952), blood transport and tissue metabolism of sex hormones (with Dr. Herbert H. Wotiz, 1953 to present), acid phosphatase and other histochemical studies in human cancer (with Dr. M. D. Reynolds, 1948 to present) and therapeutic application of cortisone and its derivatives in mammary cancer therapy (1952 to present).

ENDOCRINE CONTROL OF SEX HORMONE SECRETION

CANCER of the breast and prostate constitute the bulk of carcinomas which at times are referred to as "hormone-dependent," since they may be palliated by some type of glandular ablation or endocrine therapy. In order to understand the background for present-day treatment of these neoplasms, endocrine factors which contribute to the postnatal development of human accessory sex glands must be understood.

Hypothalamic-Adenohypophysial Control

It appears clear from observations in man and lower species that the hypothalamus acts as the primary regulator of sex hormone activity, probably partly or wholly through substances secreted into the hypophysial-portal system of capillaries which pass blood from the tuber cinereum down along the stalk of the pituitary, to sinusoids among the pituicytes of the anterior lobe (1). The human anterior pituitary gland has

no innervation so far as is known, the neural connections all passing to the posterior lobe, and occasionally into the vestigial pars intermedius. The humoral substances secreted into the hypophysial-portal system are of unknown nature. Electrical stimulation of hypothalamic nuclei, but *not* of the pars distalis of the anterior hypophysis, produces ACTH and gonadotropic hormone secretion in animals, while resection of the stalk results in disappearance of gonadotropic hormone activity, and almost all evidence of thyrotropic and adrenocorticotropic hormone secretion.

Adrenal Cortex-Gonadal Interrelations

Hormones secreted by the anterior pituitary are responsible for the stimulation of sex hormone secretion by the adrenal cortices and the gonads in both sexes. These organs originate partly from undifferentiated precursors in the embryonic mesonephric ridge and, as a result, the adrenal cortex, testis and ovary possess capabilities for biosynthesis of a similar spectrum of compounds. The nature of the chief steroid secreted at puberty will vary with the genotype sex of the gonad, with the adult differentiation of the various cell types within the gonad and with the type of stimulus exerted by hypophysial hormones. An embryonal carcinoma of the human testis, for instance, has been shown to synthesize estrone, estradiol 17 β, progesterone, testosterone and Δ-4 androstene 3,17 dione from radioactive acetate in vitro under the influence of chorionic gonadotropin (2). Human ovary and testis (as well as other body tissues) can convert androgenic steroids such as testosterone into estrogens. The human ovarian stroma up to 64 years of age appears capable of biosynthesizing estrone and estradiol 17 β in the presence of human chorionic gonadotropin in vitro (3), while corpora lutea secrete progesterone periodically throughout the years of active menstruation, and during early pregnancy. Progesterone appears to be a major intermediate of both the biosynthesis of 11-oxysteroids by the adrenal cortex, and of adrenal androgens. It has been isolated from the adrenal cortex along with some 26 other steroids, including estrone, Δ-4 androstene 3,17 dione (readily interconvertible to testosterone by cellular metabolism) and hydrocortisone. It is of interest in relation to the apparent protective effect of multiple pregnancies on risk

of mammary cancer, that human placenta is probably the chief source of progesterone, as well as of estrone, estradiol 17 β, and estriol during pregnancy, and in addition possesses enzymes necessary for synthesis of 11-oxysteroids (glucocorticoids) which are augmented during pregnancy.

Pituitary gonadotropic hormones act synergistically to stimulate secretion of testosterone by testicular Leydig cells, of estrogens by the follicular and thecal cells derived from ovarian stroma, and in many gonadectomized persons, of androgens and estrogens by the adrenal cortex. Adrenocorticotropic hormones have a triple action in augmenting secretion of 11-oxysteroids and estrogens, as well as androsterone, etiocholanolone and other 17-ketogenic steroids, some of which stimulate male sex glands and organs.

Feed-back Mechanism Controlling Hypothalamic and Adenohypophysial Activity

Of utmost importance to the clinician is the self-regulatory mechanism controlling sex hormone and 11-oxysteroid secretion by the gonads and adrenal cortices. Whenever the blood-borne concentration of metabolites of hydrocortisone, androgens or estrogens exceeds a "normal" value, adenohypophysial secretion for either ACTH or the gonadotropins is suppressed. The center for this regulatory action possibly lies in the hypothalamus. As a result of its presence, the clinician may alter at will pituitary secretion of either ACTH or gonadotropins by the administration of sufficiently high doses of cortisone or its derivatives, or natural or synthetic compounds with sex hormone activity, respectively. In most instances, the administered compound has an endocrine action clinically closely resembling that of the endogenous steroid whose secretion it suppresses and replaces, but 40–50% of cancerous breast tissues and 80–90% of prostatic cancer tissues appear to have stereospecific hormonal requirements for growth, which the exogenous agent may not provide. The action of cortisone, hydrocortisone or their newer synthetic derivatives which inhibit ACTH secretion and thereby induce atrophy of all adrenal cortical function except aldosterone secretion is unusual in that adrenal secretion of male and female sex hormones is simultaneously inhibited, leading to an endocrine deficiency which is not compensated for, in the absence of gonads.

Effects of Gonadectomy and Hypophysectomy

The presence of the gonads is necessary for the development of the accessory sex organs such as the breast and prostate during puberty. Ablation of the gonads in both sexes leads to enhanced sex hormone secretion by the adrenal cortex as a result of the above feed-back mechanism which is activated by a reduction of blood-borne sex hormones. In females, the prompt adrenal cortical secretion of estrogens (probably estrone) is adequate to maintain most of the physiologic signs of estrinization of the adult woman other than menstruation, either following castration or at the time of the menopause. In males, prostatic atrophy occurs promptly following castration, and a marked decrease in masculinization ensues, since the chief adrenocortical androgens (androsterone, dehydroepiandrosterone) whose secretion may be enhanced have less than 10% of the androgenic activity of testosterone on a weight basis. Adrenocortical androgens, therefore, are less efficient substitutes for gonadal sex hormones of the male than are the adrenal estrogens for ovarian hormones in the female.

When the pituitary stalk is severed or the anterior hypophysis is destroyed without supportive hormonal therapy, a profound and complete reduction in all sex hormone-supported activities in the body occurs. Hypophysectomy generally appears most effective of any ablative procedure in reducing estrone, estradiol 17 β and estriol secretions in females (4).

ENDOCRINE BACKGROUND FOR CARCINOMA DEVELOPMENT

Despite years of intensive research there has been no specific endocrine imbalance discovered which predisposes either to breast or prostate cancer. A previously normal history of sex hormone activity is seen in all patients with prostate cancer. Women become susceptible to breast cancer development following 10–20 years of menstrual activity as a rule, cancer occurring more frequently in nulliparous and infertile persons. Breast cancer rarely develops during pregnancy when there is maximal secretion and excretion of estrogenic hormones (along with 11-oxysteroid and progestational steroids). Most breast cancers develop during or after the menopause, at which time the progestational activity of ovaries entirely ceases, and the residual secretion of estrogen, which may

continue for many years, no longer is modified by periodic secretion of progesterone. Prostate cancer appears during the phase of waning androgenic activity, when two thirds of patients show pathologic evidence of excessive estrogenic stimulation (5). There is much experimental and clinical evidence indicating a close relationship between chronic estrogenic stimulation and mammary cancer induction; the 400:1 ratio of the disorder in females vs. males is probably attributable to relative insensitivity of the genetically male mammary duct or alveolar cells to estrogen stimulation, and to the preponderance of blood-borne testosterone which can antagonize estrogen action if present in high enough concentration. Furthermore, pathologic changes in the anterior hypophysis, ovaries and thyroid gland occur regularly in breast cancer (6, 7).

The carcinogenic action of estrogens on the female breast appears modified by progestational or other placental factors and perhaps by thyroid activity. The role of the adrenal corticoid secretions in modifying the risk of breast or prostate cancer is unknown, but there is some reason to believe that 11-oxysteroids act as estrogen antagonists, since cortisone therapy in rats can block estrogen stimulation of the uterus. Pincus *et al.* have shown a decreasing urinary excretion of biologically active estrogens in normal females with increasing age after 40, and a decrease in biologically active androgens in normal males, reaching a minimal value after the age of 65. Androgen excretion of females tends to remain constant, as does estrogen excretion of males, so that a uniform pattern of sex hormone excretion in small amounts characterized old age in noncancerous persons. The excretion of adrenal corticoids (11-oxysteroids) remains relatively constant throughout life, so that with increasing age the general anabolic action of sex hormones is less and less vigorous, while the generally catabolic activity of adrenal corticoids, or hydrocortisone, which is the principal active agent, persists.

Numerous studies have now confirmed the rapid oxidative metabolism of estrogens by neoplastic human breast and prostate tissues initially reported by Engel and his collaborators, and the exceptionally high rates of testosterone oxidation per unit cell reported by Wotiz from our laboratory for human breast and prostate carcinoma in particular. Although the results of in vitro tests must be applied with caution to in vivo problems, these and other studies suggest a rapid oxidative degradation of sex hormones by peripheral epithelial tis-

sues in addition to the liver and kidney, which appears to be excessive when carcinogenesis has occurred. Cancerous and noncancerous specimens of tissue thus far have exhibited similar pathways of steroid metabolism.

Various metabolic activities of the body also probably influence the risk of cancer in tissues where hyperplasia can be induced by sex hormones. Androgens and estrogens circulate in the blood as strongly bound conjugates of serum proteins (albumins and globulins), and it is clear that prolonged malnutrition reduces both the excretion of pituitary gonadotropins and of sex hormones, resulting in amenorrhea in females and atrophic changes in the genitalia of males.

PROSTATE CANCER

The frequency of occult prostate cancer rises steadily with the passage of each succeeding age decade after the fourth, until by the ninth decade over one half of the male survivors have developed the disease. In at least one quarter to one half of prostate cancer patients there is coexisting prostatic hyperplasia apparent by rectal examination, which unfortunately often obscures the physical findings of cancer or renders their misinterpretation readily possible by the unprepared physician. The pathologist finds evidence of benign prostatic hyperplasia in one half to three quarters of these cases, but most investigators discount any etiologic relationship between the two conditions. Prostate cancer generally begins in the posterior or peripheral parts of the gland, most remote from the urethra, but most readily palpated per rectum.

Rectal examination of the prostate is the most important means of early detection of prostate cancer and should be part of the annual physical checkup of all males over 40. A common source of error is for clinicians to attribute irregularities or nodularity of the prostate to prostatitis. While any asymmetric or irregular enlargement, whether hard or soft, in the prostate demands biopsy, one must not have blind faith in the information acquired by the examining finger. In elderly males in the Bowery series, Hudson has found an incidence of over 10% cancer by conducting serial open perineal biopsies of the prostate. Cancer was unsuspected from rectal palpation in nearly 50% of pathologically proved cases (8). As in other types of cancer, including mammary cancer, the typical hard-

ness of old established metastases may be absent in the early stages of primary tumors, when there has been relatively slight stimulation of desmoplastic reaction around the tumor. Since prostate cancer may remain localized for several years, early recognition and its resection by total prostatectomy probably prevents metastases and ultimate death. This appears to be the most important preventive aspect of prostate cancer.

The failure to utilize or properly interpret physical examination in detection of carcinoma of the prostate probably accounts for the fact that in most areas 95% of patients have regional or distant metastases when they are first detected and hence are not suitable candidates for radical resection. One half of prostate cancer patients at autopsy have primary carcinomas in other organs, notably in the colon, oral cavity, skin, bladder and stomach, which may complicate the original diagnostic problem or interfere with subsequent management.

Biopsy of the prostate gland is the only reliable procedure yet available for early cancer detection. Some clinicians have utilized the Vim-Silverman needle introduced via the perineum or rectum, but in the opinion of many urologists the chances of missing tumor tissue are much greater with this technic than with an open biopsy procedure with frozen section study. Furthermore, if cancer is found by frozen section, and metastases are not clinically apparent, a one-stage total prostatectomy may be undertaken immediately following open biopsy. The technic of open-biopsy is a safe, simple and short procedure in expert hands. The patient should, however, understand that loss or reduction of potency may result in one third or more of patients, especially if they are over 60 years of age. Although these favorable cases as yet constitute only the minority of treated prostate cancers in most clinics, their possibilities for cure and uninterrupted longevity are maximal, approximately 50% of patients living 5 years or more after complete surgical removal (Table 1). Chronic urinary incontinence may complicate the postoperative course of 10% of patients, along with impotence in all.

Should a positive biopsy be obtained and some evidence of local invasion beyond the prostate capsule be noted, either involving the bladder or the rectum, estrogen therapy may be administered for 3–6 weeks and the possibilities of total prostatectomy reconsidered at that time. Prostate carcinomas with only local invasion are likely to be quite sensitive to endocrine therapy, with sufficient tumor regression to encourage the

TABLE 1.—Survival from Initial Diagnosis in Prostatic Cancer after Various Treatments*

Stage of Neoplasm	No Therapy	Surgical Removal	Hormonal Therapy
Nonpalpable; limited within prostate capsule	70% at 5 yrs.	73% at 5 yrs.	67% at 5 yrs.
Palpable nodule; limited within prostate capsule by clinical examination		61% at 5 yrs. 37% at 10 yrs.	53% at 5 yrs. 22% at 10 yrs.
Local soft tissue metastases	10% at 5 yrs.	85% at 3 yrs. following hormonal therapy	29–43% at 5 yrs.
Distant metastases	6% at 5 yrs.		10–21% at 5 yrs.

*After Whitmore, W. F.: Symposium on hormones and cancer therapy, Am. J. Med. 21:657, 1956.

consideration of cure of some patients by total prostatectomy, following estrogen therapy. Scott has reported 85% 3-year survivals in a group of cases. These patients, with local soft-tissue invasion not yet extending to bone, also have a better prognosis following endocrine therapy alone than those with bone metastases, who have a much smaller anticipation of 5-year survival following anti-androgenic therapy.

Hormonal Therapy of Advanced Prostate Cancer

Patients with distant osseous or soft-tissue metastases comprise the largest group of prostate cancer patients seen in practice. Their advanced age, presence of other simultaneous carcinomas and frequent obstructive uropathy and nephropathy render them vulnerable to many complications in the course of treatment. Fortunately, estrogen therapy or castration are exceptionally well tolerated, and many of the complications result from the often neglected prostatic obstruction and its resulting hydronephrosis, which requires simultaneous treatment. Less than 25% of these patients, however,

will survive 5 years on endocrine therapy. Progressive hydronephrosis during endocrine therapy is a poor prognostic sign and often accompanies radiologic evidence of further bone involvement.

Total orchiectomy is the most rapidly effective anti-androgenic procedure, leading to inactivation of soft tissue or osseous metastases. Clinical benefits occur within 48–72 hours in many cases. Similar benefits result from the administration of 3–15 mg. of stilbestrol orally each day, but usually require 7–10 days before becoming fully manifest. Both forms of treatment are often simultaneously administered, since Nesbit and Baum reported that their use led to a somewhat higher percentage of 3-year survivors (66%) than with either procedure alone (50–53%). Scott advocates the initial administration of stilbestrol, as long as clinical benefit takes place, followed by orchiectomy when relapse commences (9). He believes there is less likelihood of adrenocortical hyperactivity and subsequent cancer stimulation by adrenal hormones when orchiectomy is performed in a well-estrinized patient rather than in the untreated patient. General clinical experience indicates that prostate cancer reactivating following stilbestrol therapy is less likely to respond to other types of estrogen, probably as a result of overgrowth of endocrine-independent elements in the tumor. However, other estrogens are often tried with some palliation in individual cases (Table 2). It is well to terminate stilbestrol therapy when relapse occurs and observe for 2–3 weeks before starting additional treatment, since temporary remission may occur simply as a result of estrogen withdrawal, and also has been reported following testosterone therapy.

Total adrenalectomy has been performed for advanced prostate cancer relapsing after castration and estrogen therapy; this procedure should not even be considered in the 10–20% of patients who fail to benefit initially from hormonal therapy, since these patients probably have carcinoma of such undifferentiation that autonomy has resulted. Total adrenalectomy is a major operative procedure of considerable risk in the elderly patient, and probably should not be considered after the age of 60–65. Most clinics have given up its use, since although symptomatic improvement and diminished serum acid phosphatase activity may be achieved, demonstrable objective improvement in soft-tissue or osseous lesions rarely follows.

Scott has pointed out that the administration of 100 mg. cortisone daily to gonadectomized males depresses adrenal androgen (androsterone and etiocholanolone) excretion to trace levels in all cases, comparable to values noted following adrenalectomy. Our experience has been comparable in females. As yet, Scott has seen no patient in whom adrenalectomy would be required because cortisone therapy did not practically eliminate residual adrenal androgen excretion, and he recommends this form of endocrine therapy in all patients who relapse during estrogen therapy or after castration. Miller and Hinman report local tumor regression in 60% of their cases, and improvement in bone pain on 50–100 mg. cortisone daily (after discontinuing previous estrogen therapy) (10). Doses greater than 100 mg. cortisone daily should not

TABLE 2.—COMPOUNDS USEFUL FOR ENDOCRINE THERAPY OF ADVANCED PROSTATE CANCER

COMPOUND	DAILY DOSE	REMARKS
Ethinyl estradiol	0.5 mg. b.i.d. or t.i.d.	
Stilbestrol	3.0–15 mg.	Drug of choice for initial therapy
Trianisyl-chlorethylene (TACE)	24–180 mg.	May be effective in controlling relapse following stilbestrol therapy and castration. Lacks usual estrogen side effects such as nausea, mastalgia, edema
Cortisone	12.5–25 mg. q.i.d.	May control relapse after estrogen and castration; may shrink primary tumor and relieve bone pain for average period of 3 mos.

be exceeded, in view of its 6–10% transformation to androgenic metabolites. If one administers 200–300 mg. cortisone daily, urinary androgenic metabolites in adrenalectomized castrate males actually exceed those noted preoperatively (11). Prednisone therapy in 30 mg. daily doses inhibits adrenal androgen excretion equally as well as 100 mg. cortisone and is far less likely to be converted to androgens. Simultaneous estrogen administration along with adrenal corticoid therapy is probably unnecessary in the castrate male, and may interfere with a good result. After several weeks of cortisone

or prednisone therapy, 60–90 mg. of desiccated thyroid daily may be necessary to prevent hypothyroidism (see Table 8).

In summary then, hormonal therapy of advanced prostate cancer is best conducted by serially utilizing

1. Stilbestrol therapy 3–15 mg./d.
2. Orchiectomy, either initially or subsequently.
3. Trial of other types of estrogens, such as TACE, when patient relapses.
4. Cortisone therapy 50–100 mg./d. or prednisone 30 mg./d. to the castrate patient, as the terminal form of palliation.

Concomitantly with hormonal therapy, x-ray therapy should be administered where necessary for the control of local disease, painful osseous metastases or perineural metastases. The local injection of radioactive substances into the cancerous prostatic tissue has been utilized in several clinics, with marked subjective relief and shrinkage of tumor. This requires specialized equipment and trained personnel, and thus far there is no definite evidence that such therapy is superior to local x-ray therapy, or that it increases longevity. Intravenous Mustargen or oral triethylene melamine in courses may be of use in the control of widespread metastases which cannot be controlled by roentgen therapy alone.

Endocrine treatment of advanced prostate cancer has increased the 5-year survival rate of patients as well as adding greatly to their comfort and well-being, with at least 75–80% responding initially to endocrine therapy.

Some correlation has been reported between initial fractionated androgen excretion in these patients, and the likelihood of clinical response (Table 3). Androsterone and etiocholanolone represent two major urinary excretory 17-ketosteroid metabolites of testosterone which are also derived from the adrenal cortex. Dehydroepiandrosterone, the third major 17-ketosteroid metabolite, is of exclusively adrenal origin. Patients most likely to respond to castration therapy for prostate cancer have well-preserved androsterone and etiocholanolone excretion compared with patients who fail to respond. Castration reduces excretion of these two urinary steroids, by one-half, the remainder originating from the adrenal cortex. Cortisone therapy by suppression of the latter further reduces the urinary concentration of these steroids to trace levels. Androsterone and dehydroepiandrosterone, however are far less potent androgens than testosterone, so that

TABLE 3.—Relationship Between Endocrine Therapy, Suppression of Androgen Excretion and Clinical Response of Prostatic Carcinoma

Source	Hormone	No. Patients	Condition	Therapy	Urinary Excretions	Clinical Benefit
Hellstrom *et al.*, Acta endocrinol. supp. 31:261, 1957	17-Ks	10	Normals	0	7.2 mg./24 hrs.	
		21	Ca prost.	0	3.5 mg./24 hrs.	
	Androsterone and etiocholanolone	10	Normals	0	4.3 mg./24 hrs.	
		21	Ca prost.	0	2.1 mg./24 hrs.	
		12	Ca prost.	0	0.86 ± 0.22	
				Castration	0.62 ± 0.28	None
		5	Ca prost.	0	1.72 ± 0.74	
			Ca prost.	Castration	0.98 ± 0.28	Slight remission lasting 3–19 mo.
		16	Ca prost.	0	3.18 ± 1.04	
			Ca prost.	Castration	1.08 ± 0.38	Excellent remission 3–30 mo.
Burt *et al.*, Cancer 10:825, 1957	Androsterone and etiocholanolone	2	Ca prost.	0	2.12	
				Castration	1.90	Fair to no remission
		4	Ca prost.	0	4.78	
				Castration	1.90	Good remission
		4	Ca prost.	Castration only	2.65	
				Castration + stilbestrol B	1.79	
		1	Ca prost.	Castration + stilbestrol + cortisone 100 mg./d added	3.8	
					0.22	

one cannot expect as striking a cancer response to the complete elimination of androsterone and other adrenal androgens by cortisone therapy, compared with the effects of reduction of testosterone secretion by castration.

Special Therapeutic Problems in Prostate Cancer

Hemorrhagic disorders.—Bleeding may become a primary problem in case management, occasionally spontaneously and more often following genitourinary instrumentation or surgery. If the prothrombin time and platelet count are within normal limits, excessive fibrinolytic activity and fibrinogenopenia may be the etiologic factors. Prostatic secretion contains fibrinolytic activity which lyses the seminal coagulum; cancerous prostatic tissue is frequently rich in some component of this fibrinolytic system, which is capable of destroying normal blood clot. Persistent oozing from venipuncture sites, extensive purpuric lesions in the skin, in addition to frank hemorrhage should alert the clinician to the possibility of excessive fibrinolysis, which is readily diagnosed by drawing off blood in a test tube, allowing it to clot (which will occur in the normal time) and then observing to what extent the clot will become partially or wholly liquefied within the next 1–24 hours. Blood transfusions are often required when fibrinogen is not available for therapy. These measures alone may not adequately counteract continued fibrinolytic activity, unless either 200–400 mg. toluidine blue is given orally daily, or 1.0 cc./15 lbs. body weight of 7–8% n-butanol in saline is given intramuscularly every 4–6 hours (12). Hypoprothrombinemia as a cause of hemorrhage should be treated with large doses of parenteral vitamin K_1 oxide and transfusions of fresh blood. The use of excessive amounts of distilled water for irrigation during cystoscopy undoubtedly contributes to hemorrhagic disorders, as well as producing a hemolytic anemia which may seriously impair renal function.

Feminization.—Prolonged estrogen therapy with estradiol or stilbestrol results in feminization of the elderly male manifested by emotional lability, gynecomastia, increased fat distribution over the buttocks and breasts and absence of libido and potency. Cancer may appear in the estrogen-stimulated hyperplastic breast after years of therapy, and should be

closely watched for. These adenocarcinomas should be cured by early recognition and radical mastectomy if possible, but if they are too far advanced, or the patient is in precarious physical condition as a result of his other disease, local irradiation and prednisone therapy may be used, along with castration if this has not yet been done. In the past, these primary breast cancers have been considered to be metastases from the prostate, despite the great rarity of involvement of the breast in either sex by any kind of metastatic carcinoma or sarcoma, because of the large amount of acid phosphatase present in the tumor. This enzyme, however, has been found in high activity in many types of adenocarcinoma, including breast (13).

CONTROL OF URINARY TRACT INFECTION.—Obstruction, insertion of foreign bodies in the urinary tract, open wounds following prostatic resection, and concomitant carcinoma all contribute to the universal problem of ascending pyelonephritis and its control in these patients. "Prophylactic" antibiotic therapy is no substitute for rigid asepsis and minimal use of indwelling catheters in prevention of clinical infection; excessive use of broad-spectrum antibiotics may lead to replacement of sensitive flora by mixed flora containing predominantly *Aerobacter aerogenes* and *Pseudomonas aeruginosa* which may prove refractory to all therapy and hard to control should tissue and/or blood invasion develop. Whenever possible, sulfonamide agents should be used to suppress the growth of mixed flora, with blood levels sufficiently high to control interstitial renal infection. The broad-spectrum antibiotics may then be used to control episodes of bacteremia and acute pyelonephritis by predominant strains which are usually sensitive to one or more antibiotics which have been held in reserve for such complications. Examination of freshly voided specimens for pus casts, and the use of colony counts as part of the bacteriologic technic will aid in evaluation of the degree of pyelonephritis, since more than 5,000–10,000 organisms per cc. have been shown to be associated with significant pyelonephritis at autopsy. Pyelonephritis is usually the final insult causing decompensation of the hydronephrotic kidney, or in preventing its recovery of function once urinary obstruction has been relieved, in many terminal cases. In many cases, there will be enough urinary tract pathology to make it impossible to wholly eradicate chronic infection, and it is in these cases that Gantrisin therapy 2.0–4.0 Gm. or

Kynex 1.0 gm. daily will often be of great value in suppressing nearly all clinical manifestations of bacterial invasion into the tissues.

CARCINOMA OF THE FEMALE BREAST

Diagnosis

Breast cancer seldom manifests any local symptom other than a painless tumor mass in the breast, most frequently noted by the patient herself. Occasionally, bleeding or other discharge from the nipple, or a change in appearance of the nipple ("eczema"), will bring the patient to the physician. All women over 30 should practice periodic breast self-examination, preferably a day or two before each menstrual period, for the presence of suspicious nodules. Since there is a strong family inheritance of mammary cancer, women with one or more relatives with this disease should in addition have their breasts examined by a physician every 6–12 months. Despite a great deal of public and professional education, over one half of patients still have axillary or other metastases by the time they reach a surgeon for consideration of operation. There has been little improvement in death rates for breast cancer during the past quarter century.

Multiple nodules in both breasts which tend to be enlarged or painful premenstrually usually represent some type of mammary dysplasia, gathered under the loose clinical term of "chronic cystic mastitis." Localized areas suggestive of infiltration, or any nodules which appear to be unusually conspicuous in breasts of women with cystic mastopathy, must be biopsied for initial diagnosis. As a rough rule, most breast biopsies in those under 40 result in benign lesions while above 50 most biopsies contain carcinoma. The patients with benign disease should be followed up at 3–6 month intervals, with re-biopsy whenever sufficient abnormality occurs. They often appear to be unusually labile emotionally, and if married may be relatively barren, with only 1 or 2 pregnancies. This breast condition tends to regress clinically after the age of 50, but is associated with a much higher risk of breast cancer than the woman whose breasts are free from abnormal nodules during her menstrual years. Therapy with human chorionic gonadotropin, as well as testosterone is reported to temporarily reduce these precancerous breast changes (14).

Intraductal papillomas of the breast are regarded by some as precancerous lesions, occurring as they often do about 10 years earlier than mammary cancer, and sometimes possessing metaplasia and anaplasia. They may be so soft as to be palpable with difficulty, but give rise to nipple bleeding as a sign of disease meriting breast exploration.

Surgical Treatment

If the patient does not have (a) extensive inflammatory carcinoma; (b) involvement of supraclavicular lymph nodes; (c) axillary lymph nodes more than 2.5 cm. in diameter or those which are fixed to the thorax; (d) extensive ulceration of the tumors, or fixation to the thorax; (e) widespread cutaneous metastases; (f) edema of an arm, or of the breast; or (g) distant metastases by x-ray, in lung or bone, a classic type of operation following the Halstead principles of radical mastectomy should be performed following positive biopsy. We would still favor radical mastectomy for any cases lacking these contraindications which are diagnosed during pregnancy or lactation. Extension of the radical operation to internal mammary lymph nodes offers only slight increase in chance of cure, at a considerable increase in morbidity, and is not widely practiced. There is much debate concerning the management of tumors of borderline operability. Many patients appear to benefit in a palliative sense from radical mastectomy, since they remain free of disease in the breast or axilla, despite recurrences elsewhere.

McWhirter has reported impressive 5-year survivals in patients receiving simple mastectomy followed by postoperative hormonal and irradiation therapy directed at the axillary, supraclavicular and internal mammary lymph nodes, as a means of treating the type of patient referred to his clinic (Table 4). While every patient whose tumor appears to be resectable should be granted the chance of cure offered by radical surgery, the clinician should utilize more fully the palliative procedures of simple mastectomy and radiotherapy when cure cannot be anticipated (15). Competent surgical advice is required to separate patients deserving radical surgery from those in need of palliative procedures. The results of surgical therapy appear closely related to the stage of disease at the time of treatment (Table 4).

Although satisfactory figures are not available for statistical proof of improved symptom-free survival following postoperative irradiation, this should be administered whenever a subareolar or inner quadrant tumor mass has been removed,

TABLE 4.—ABSOLUTE 5-YEAR SURVIVAL RATES FROM INITIAL DIAGNOSIS OF BREAST CANCER
(Absolute recurrence-free rate usually 3–9% lower than survival rate)

INITIAL CLINICAL STAGE OF DISEASE	TREATMENT			
	None	Radical mastectomy	Simple mastectomy plus radiation therapy plus x-ray castration plus hormone R	Recurrent disease after radical mastectomy plus radiation R plus hormone R
Limited to breast		63–82% } 59–72%	75% } 67%	
Palpable mobile axillary nodes		44–57% }	47–58% }	
Axillary and/or other local metastatic disease		16–39%	30%	
Metastases distant from breast		5–7%	4%	
All stages	0–20%	34.6–48% (recurrent cases 31%; nonrecur. cases 51%)	42–51% (residual disease presumed present all cases)	15–30%
	(5% at 10 yr.)	(20.7% at 10 yr.)		(4.3–8% at 10 yr.)
Source of statistics	Daland (15) Haagenson (31) MacDonald (31)	Shimkin (32, 33) Smithers (15) Haagenson (31) Garland (31)	Garland (31) McWhirter (34) Ackerman (35)	Lemon (20, 27) Shimkin (33)

or when axillary metastases have been extensive. At least 3,000–4,000 r should be given to each of three fields in the axillary, supraclavicular and internal mammary areas.

In our clinic, we do not advise prophylactic oophorectomy in pre- (or post) menopausal females with axillary lymph node metastases, although there is evidence from two clinics

that such procedures enhance life expectancy. Prophylactic oophorectomy alone does not seem to prevent fulminating early postoperative metastases, and its use may prevent subsequent palliation of established metastatic disease. However, all patients with inflammatory carcinoma should have oophorectomy or hypophysectomy as soon as the diagnosis is made. The former operation may also be considered if there is any possibility of additional pregnancies, which should be avoided by postoperative breast cancer patients until at least 3 years' well-being has been achieved.

Hormonal Therapy of Advanced Breast Cancer

Between 50 and 70% of women at the time of mastectomy have axillary or other lymph nodes involved by cancer, and can be expected to develop recurrent disease within a few months, or as long as 20 years after mastectomy. The first symptoms of recurrent disease may be extremely varied, since any organ or tissue may be first involved by metastases. As a rule, however, either local recurrences or osseous metastases make themselves known in ½–⅔ of patients as the initial manifestation of recurrence, usually within 2–3 years after diagnosis. Metastases in the lung, liver or brain have a much more serious prognosis than lymphatic, osseous or superficial skin metastases, but may respond extremely well to treatment nevertheless, for periods up to 1 year.

The presence of metastatic cancer should be verified pathologically whenever possible, before the patient or the family are informed. When lymph nodes or cutaneous lesions are not available for biopsy, bone marrow examination by a competent hematologist may confirm the diagnosis.

Local irradiation using either 250 kv. or supervoltage machines is the first line of defense against metastases, before hormonal therapy. Prophylactic irradiation should be administered to defects in weight-bearing bones, especially in the spine or femora. At least 2,000–3,000 r per portal, with use of 2 or 3 portals, can be safely used against osseous metastases, while lymph nodes may only require this dose through 1 portal for palliation. Extensive irradiation over cartilagenous areas, small intestine or lung should be avoided due to the deleterious action on these radiosensitive tissues.

Oophorectomy.—The first step in endocrine therapy of

mammary carcinoma should be taken when it is apparent that the systemic activity of breast cancer metastases is exceeding the capacity of x-ray therapy for control, and oophorectomy is the initial procedure of choice. Surgical castration is more certain of preventing further ovarian estrogen secretion than radiation therapy to the ovaries. Most investigators agree as to the need for castration of all premenopausal females, but few as yet are willing to advise this procedure to menopausal (less than 1 year since last menstrual period) or postmenopausal females. Objective benefits are seen 4–5 times more commonly after oophorectomy in premenopausal compared with postmenopausal females, but Smith and Smith have published statistical evidence suggesting that oophorectomy of patients in their 6th and 7th decades of life increases longevity nearly twofold (16). In our clinic, we recommend oophorectomy in all patients with distant uncontrolled metastases, up to the age of 65–70 in the belief that this slows metastatic growth, may fulfill conditions necessary later for the most effective use of adrenal steroids in therapy, and because the clinical response to oophorectomy is the best single piece of evidence we have indicating the hormonal dependence of the cancer. No steroids should be administered if possible less than 6–12 weeks after oophorectomy, in order to clearly evaluate the effects of ovarian ablation. As a result of the postoperative stress response mediated via the adrenal glands, however, transient symptomatic exacerbation of disease may occur during the first 3 weeks after surgery, and is best treated by the administration of prednisone 30–40 mg. for 2–3 weeks, if necessary in the rare case.

TESTOSTERONE THERAPY.—Loeser first showed in 1938 that testosterone injections favorably altered the growth of breast cancer, and large series of cases have been reported since then, which have confirmed the usefulness of this form of hormonal therapy. Testosterone in whatever form used must be given in doses adequate to suppress endogenous pituitary gonadotropic secretion (17); the long-acting preparations should not be used for initial therapy. No preparation superior to testosterone propionate 50–100 mg. thrice weekly intramuscularly has been found as yet, although a number of related compounds have also been of significant palliative benefit (Table 5). Testosterone may be administered to patients regardless of age but always with due respect for its masculinizing and sodium-retaining properties. This agent should not

be administered until any oophorectomy remission has run its course. Once initiated and found to be of benefit, it should be continued for as long as any sign of a clinical remission persists. Approximately 20% of osseous lesions may respond

TABLE 5.—Compounds Useful for Endocrine Control of Advanced Mammary Cancer

Compound	Daily Dose	Remarks
Testosterone propionate	150–300 mg. IM weekly	About ⅓ of osseous or soft tissue lesions respond; may be used at any age
Stilbestrol or estrone sulfate	5.0–15 mg. PO 2–3 mg. IM q.i.d.	About ⅓ of osseous, ½ of soft tissue lesions respond. Use only in patients over 55–60 yr.
Fluoxymesterone	20 mg. PO daily	Somewhat less virilizing than testosterone and probably not so effective. Reported to induce remissions in patients relapsing after hypophysectomy
Cortisone	12.5–25 mg. q.i.d. PO	Usually ineffective in patients under 65 who have not been oophorectomized. About ¼ of osseous lesions respond, and ⅖ of soft tissue lesions. Low-salt diet necessary only in cardiac patients.
Prednisone	10 mg. t.i.d. PO	Same precautions as for cortisone and similar effectiveness. Agent of choice for hypercalcemia. Sodium restriction usually unnecessary.
Triamcinolone	8 mg. t.i.d. PO	Preliminary studies indicate same effectiveness as prednisone
Depot forms of long-acting androgens or estrogens		Very hazardous for initiation of therapy, but may be utilized after first 6 weeks of treatment if remission has developed

temporarily to testosterone therapy, although progression of lesions is often noted in some areas, during recalcification in other areas. Soft-tissue lesions may respond equally frequently. About one half of the patients treated have subjective improvement, with improvement in strength, appetite and weight gain, so that there is a wide discrepancy between sub-

jective and objective response. A minimal trial period of 3–4 weeks' therapy is recommended, since transient exacerbation of symptoms may take place during the first 10–14 days of treatment, or improvement may be delayed.

At the dosage level necessary, masculinization is to be anticipated in all patients, with more striking manifestation in brunettes (Table 6). Increased hirsutism, increased muscle

TABLE 6.—SIDE EFFECTS OF ANDROGEN THERAPY AND THEIR CONTROL

SIDE EFFECT	MEANS OF AVOIDANCE OR CONTROL
Hirsutism, other signs of virilization in +95%, including temporal hair recession, hoarseness, increased muscle development of arms, acne and skin flushing	Epilating procedures
Polycythemia in 30–40%	None necessary
Increased libido, 37%	Reduce frequency or dosage of injections
Hypercalcemia secondary to increased osteolytic activity, 10%	Stop androgen, maintain ambulation and urine output of at least 1,000–1,500 cc. daily, give adrenal corticoids
Edema, 16%	Sodium restriction, diuretics

mass on arms, temporal hair recession and redistribution of body fat depots from buttocks and breasts to the abdomen are among the more striking physical changes. About 40% of women notice a marked increase in libido which accompanies hypertrophy of the clitoris. Increased flushing of the face and exposed areas of the neck and upper sternum may occur. Amenorrhea will be induced in those with functional ovaries. The hematocrit and hemoglobin concentration may become significantly elevated in a third or more of patients.

The hazardous effects of treatment are chiefly those related to stimulation of osteolytic metastases, with development of hypercalcemia. Hypercalcemia has occurred in nearly 10% of some series of advanced cases, and is far more frequent when bedridden cases are treated. The symptoms of anorexia, vomiting, abnormal (sweetish) metallic taste, prostration, weakness or coma should alert the clinician to hypercalcemia. The most rapid confirmatory test is an EKG, which may show a very short QT interval in cases with normal serum K. Treat-

ment of hypercalcemia is best carried out by terminating sex hormone therapy, followed by administration of IV dextrose and water and/or saline to insure diuresis, and the administration of 200–300 mg. cortisone daily or preferably 30–40 mg. prednisone daily (18). Sodium retention and edema may also occur with the risk of cardiac decompensation in patients with heart disease.

The mean duration of testosterone-induced remissions is about 9 months. Once patients have had testosterone therapy and have relapsed, further treatment with a similar preparation is unwise. Withdrawal of the steroid may lead to transient subjective improvement in relapsed cases.

ESTROGEN THERAPY.—In 1944, Haddow and co-workers reported the clinical effectiveness of stilbestrol in mammary cancer which has been widely confirmed by subsequent investigations. This synthetic estrogen has been most useful in producing remissions in the older patients, usually those who are 5 years or more beyond the menopause (55 years or older). Between 40 and 50% of soft-tissue lesions may respond to therapy, and 20% or more of osseous lesions may show recalcification. The chief side effects are nausea and anorexia noted by at least half of the patients treated, water and salt retention and intermittent vaginal bleeding (Table 7). Adverse symptoms are particularly common during the first 2 weeks of treatment, even in those who later develop exceptional remissions. The short-term response to stilbestrol has been made the subject of the stilbestrol stimulation test for determination of tumor hormone dependence, using urine calcium excretion as an indirect index of increased tumor growth. This test, however, carries some risks and it yet remains to be proved that it is statistically valid as an indicator of subsequent responsiveness to other types of treatment.

The diphasic response to stilbestrol therapy, with initial exacerbation followed by regression in a high percentage of elderly patients, means that therapy must be continued at least 1 month before it can be evaluated. Hospitalization may be necessary in some patients to tide them over the initial period of anorexia and nausea, and the occurrence of hypercalcemia must be closely watched for.

The diphasic response to estrogen therapy also suggests that its actions are indirectly mediated via inhibition of pituitary gonadotropin secretion and the resulting depression of sex hormone excretion from the gonads, and the adrenal cor-

tex, as Scott has shown. Reduction of gonadotropin excretion to low or undetectable values uniformly occurs with the use of 5–15 mg. daily doses of stilbestrol within a week or 10 days, which is approximately the duration of the initial phase of its diphasic effect on breast cancer. Loraine has found that patients whose gonadotropin excretion is markedly elevated

TABLE 7.—MAJOR SIDE EFFECTS OF ESTROGEN THERAPY AND THEIR CONTROL*

SIDE EFFECT	MEANS OF AVOIDANCE OR CONTROL
Nausea in 57% of females, lasting 1–2 weeks or more, less severe in males	Inject estrogen parenterally, using 5–10 mg. estrone sulfate weekly; give chlorpromazine or compazine
Fluid retention in 35% of elderly females, less common or severe in males	Low-sodium diet, diuretics
Uterine bleeding in 40%	Temporary cessation of therapy 2–3 weeks
Urinary urgency and incontinence (28%) (females)	Empty bladder by the clock
Hypercalcemia as result of tumor activation (breast cancer only)	Terminate estrogen, maintain ambulation and urine output of at least 1,000–1,500 cc. daily, give adrenal corticoids
Gynecomastia in over 80% of males	Inadvisable to change therapy during remission
Emotional lability, impotence in males	Symptomatic therapy
Purpuric lesions on forearms, dorsum of hands (males)	None

*After Kennedy, B. J., and Nathanson, I. T.: Effects of intensive sex steroid hormone therapy in advanced breast cancer, J.A.M.A. 152: 1135, 1953.

above the age-corrected normal value before therapy usually do not obtain clinical remissions from stilbestrol treatment (19). These patients presumably already manifest a low concentration of endogenous blood-borne estrogens which has led to augmented pituitary gonadotropin secretion, probably because of aging processes or metastases which have impaired the secretory capacities of the adrenal or gonads. Patients whose gonadotropin excretion is close to normal have suffi-

cient endogenous estrogen secretion to maintain partial inhibition of additional gonadotropin secretion.

No estrogenic agent superior to stilbestrol in clinical effectiveness has yet been developed for breast cancer therapy. A number of steroid compounds have recently been developed which have only feeble estrogenic or androgenic potency but anabolic or progestational or other properties. These have not yet been clearly shown to be more useful than stilbestrol for breast cancer treatment, and in the case of one compound (Nilevar—norethandrolone (17-alpha-ethyl-17-hydroxynorandrostenone) there has been noted frequent impairment of hepatic function. Until much more is known about the newer derivatives of androgenic, estrogenic and progestational steroids which are now flooding the market, one should be cautious in abandoning the use of compounds of known though limited effectiveness in cancer therapy. The same conservatism should be practiced with respect to the many new adrenal corticoid derivatives now available, whose use is discussed later.

Estrogenic therapy of breast cancer has been most effective in patients over 60; below this age, the younger the patient the more often one encounters disease stimulation during treatment. Estrogens should not be administered following cortisone therapy, adrenalectomy or hypophysectomy, since remissions are quite rare, and the risk of rapidly fatal disease reactivation is great. Nathanson believed that estrogens through their action on connective tissues sensitized lesions to roentgen irradiation, but this has not been observed by others. Estrogen-induced remissions last 1 year on the average.

CORTISONE AND PREDNISONE THERAPY.—Following oophorectomy in patients under 65, and attempted palliation by androgens and/or estrogens, medical inhibition of adrenocortical function appears to be the ultimate medical approach to disease control.

Unlike sex hormone therapy, in which extraordinarily high and unphysiologic hormonal doses have been required for remissions, modest dosage of adrenal cortical hormones appears to be mandatory for prolonged effectiveness (20). Sex hormones have a natural limitation on their action on the body, which places a ceiling on the amount of masculinization or feminization which can be induced at any dosage level. It may be that serum protein transport of sex hormone conjugates permits only a limited amount of tissue activation, the re-

mainder of the compound being excreted in the bile and urine as an inactive substance. It is well known both experimentally and clinically that catabolic activities of cortisone and hydrocortisone are dose-dependent, with increasing manifestations of general body "toxicity" with excessive administration of these steroids, comparable to the changes seen in Cushing's syndrome. Protein catabolic phenomena are especially augmented, which represent an even greater burden to the protein-starved tissues of the cancerous patient. Steroid-induced diabetes may appear, disorders of electrolyte metabolism become more frequent and the catastrophic hazards of infection, perforated or bleeding peptic ulcers and of major psychoses become common with dosage of 200–300 mg. cortisone daily or 50–100 mg. prednisone daily, over several weeks or months. In addition, excessive dosage of corticoids leads to inhibition of fibroplasia which is one of the few natural defenses to metastases, and immunologic defenses to infection are decreased as a result of the lympholytic action of corticoids. Finally, the administration of large doses of cortisone or hydrocortisone defeats the very purpose of such therapy, which is to minimize the endogenous pool of sexually active hormonal metabolites, because several observers have found that with doses of 100 mg. daily, a significant conversion of cortisone occurs to androgenic metabolites such as 11 beta hydroxyandrosterone and 11 keto etiocholanolone (11). Since androgens appear readily convertible to estrogens by numerous tissues, it is possible that a secondary conversion to estrogens may take place. The higher the dose of cortisone, therefore, the more likely it will be that androgenic and estrogenic metabolites will be formed in time which will nullify any anticancer activity. Between 50 and 100 mg. cortisone or hydrocortisone administered daily as divided doses every 6 hours, or 20–30 mg. prednisone daily or prednisolone similarly administered will result in maximal inhibition of adrenocortical sex hormone excretion, with minimal possibilities for conversion to hazardous metabolites, or for toxic sequelae to develop during prolonged therapy.

Another equally important difference between sex hormone therapy and corticoid therapy is the entirely opposite effect on pituitary gonadotropin secretion. Segaloff has shown the correlated relationship between clinical effectiveness of various androgenic steroids in breast cancer therapy, and their capacity to inhibit pituitary follicle-stimulating hormone secretion

(human menopausal gonadotropin) (17). Cortisone therapy, however, when administered to noncastrate females by several observers caused a transient increase in follicle-stimulating gonadotropin excretion over a period of several weeks followed by a return to previous values. This ovarian-stimulating property of cortisone has proved of great value in the restoration of menstrual cycles in some young females with congenital or acquired adrenocortical hyperplasia and virilization, when modest therapeutic doses of 25–75 mg. per day were administered by Wilkins and his associates. However, this action of cortisone largely negates its effect in cancerous women with functional ovarian tissue, since the ovaries before or after the menopause may be stimulated by enhanced gonadotropin activity to secrete more estrogens rather than less, and perhaps compensate entirely for any reduction achieved in adrenocortical estrogen excretion. Stoa and Knutsen have shown that cortisone therapy in the intact female does not significantly reduce total estrogen excretion (21), while Smith and Emerson, among others, have reported a marked decrease in oophorectomized women (4, 22). The surgical absence of the ovary prevents its compensatory estrogen secretion resulting from enhanced pituitary gonadotropin activity. In oophorectomized patients receiving adrenal corticoids, urinary gonadotropin excretion rises to persistently elevated levels lasting for months or even 1 or more years, and resulting hot flashes may persist for equally long periods.

The first brief clinical effects of cortisone on mammary cancer were reported in 1954 by Pearson and colleagues, using doses ranging from 75 to 300 mg./day (23). About one half of the small number of cases reported were palliated objectively by recalcification of osteolytic foci and regression of soft-tissue metastases. The smaller doses were less effective in non-oophorectomized patients, and remissions lasted not more than 3 months. During this period, negative results were reported by Segaloff, Taylor and others, who did not oophorectomize their patients. Nissen-Mayer in Norway (24), and we in the United States in 1956 reported series of cases with 50–65% objective benefit in patients who were previously oophorectomized up to the age of 65 (20), with confirmatory case reports from a number of other clinics and physicians.

Prednisone, when it became available, was shown to provide maximal adrenocortical inhibition in doses of only 30 mg. daily, a dosage level at which minimal conversion to an-

drogen could be expected. Taylor and his group in 1957 reported objective remission in a number of cases with central nervous system metastases with prednisolone therapy, despite neglecting oophorectomy in most of those patients (25). Previously, Taylor and his group reported that retention of ovaries apparently reduced the clinical effectiveness of adrenalectomy in his clinic (26). Prednisone therapy 30 mg. daily in our experience results in 50% objective remissions in both soft-tissue and osseous metastases, with better results in our series where oophorectomy has been practiced until age 65 than in two series of nonoophorectomized patients reported by others (27). Using the dosage range between 20 and 30 mg. daily, the average duration of prednisone-induced remissions has been nearly 10 months in our series, while Taylor's group, utilizing 50–100 mg. daily doses, noted only exceptional remissions lasting more than 12 weeks. Thus far, in collected series from all sources of cortisone and prednisone therapy, the mean objective remission rates appear to equal those reported in all available collected series of adrenalectomy and hypophysectomy (27). It is therefore reasonable to suggest that much of the postoperative benefit attributable to ablative procedures is partly the result of the postoperative corticoid therapy. Estrogens or androgens should never be given along with corticoids therapeutically.

Thyroid substitution therapy probably controls one of the many side-effects of adrenal corticoid therapy, which is attributable to depression of thyroid function (Table 8). After long-continued therapy with prednisone, it is possible that relapse occurs when the metabolic processes of the body adapt in such a way that the double-bond of this steroid has become saturated, resulting in degradation to cortisone, which would then result in an ineffective adrenal suppressive dose. In two or three patients who have relapsed, we have suspected such a metabolic adaptation, and have obtained some additional palliation by changing therapy to hydrocortisone 100 mg. daily to insure continued adrenal cortical suppression.

The most durable remissions induced by adrenal corticoid therapy have occurred in women between 40 and 70, although briefer palliation has been seen in younger patients. Patients who have had oophorectomy performed over 6 months before treatment has been started have the most favorable prognosis, which includes most of those who have objectively benefited by this procedure. However, the effectiveness of previous sex

TABLE 8.—Side Effects of Low-Dosage Adrenal Corticoid Therapy

Side Effect	Means of Avoidance or Control
Facial rounding in all patients	None
Buffalo type of trunk obesity, excessive weight gain	Diet restriction
Hot flashes in one half of patients (those who have had hot flashes during menopause)	Indicate relative estrogenic deficiency induced by appropriate dosage (*Do not give any estrogens*). Phenobarbital 15 mg. t.i.d.
Loss of libido in some women under 45	None
Insomnia in 20–25% during early weeks of treatment	Equinil 0.8 Gm. at bedtime
Purpuric lesions on forearms, hands in 10% of cases	None
Muscular weakness, especially of thighs	2–3 Gm. potassium chloride daily or 4.0 cc. potassium triplex solution t.i.d.
Glycosuria in about 5% of patients	Low-carbohydrate, low-fat, high-protein diet, Orinase 1.0–1.5 Gm. daily if glycosuria persists, or insulin
Latent or overt hypothyroidism with low RaI uptake, low serum protein-bound iodine in 5% of patients	Desiccated thyroid 90 mg. daily
Peptic ulcer in less than 5% of patients	Prophylactic ulcer management; may necessitate termination of therapy

hormone therapy is not reliable in predicting the chances of remission induced by adrenal steroid therapy.

Total adrenalectomy following oophorectomy.—Huggins in 1945 and subsequently showed that total adrenalectomy removed a source of sex hormones stimulating carcinoma of prostate and breast following reactivation in castrated patients, thereby adding to his already monumental contributions to cancer therapy. When cortisone became available for postoperative maintenance therapy, the long-term results of total adrenalectomy could be assessed and objective improvement in both osseous and soft-tissue metastases have

been described in about 40% of advanced mammary cancer patients. Total adrenalectomy is a major surgical operative procedure, and the totally adrenalectomized patient requires careful supervision of cortisone maintenance therapy, which is usually in the range of 50–75 mg. daily, but which must be increased to 200–300 mg. daily should major infection, trauma or another operation precipitate acute adrenal insufficiency. More than 30% of all patients have accessory adrenocortical tissue in the retroperitoneum or kidneys, and hence only subtotal resection is possible in this group. Total adrenalectomy appears to give best clinical results in patients between 35 and 60. Huggins has reported remissions in several patients with inflammatory breast cancer, which seldom respond to any type of therapy. Adrenalectomy without oophorectomy is relatively ineffective according to Taylor. Sex hormone therapy may be palliative before but seldom following adrenalectomy. The response to previous oophorectomy again appears to provide the best indication of benefits expected following adrenalectomy. Numerous studies have shown that total adrenalectomy and oophorectomy cause only a partial reduction of urinary estrogenic activity (4) (Table 9). If adrenalectomy is recommended only in patients who have demonstrated an objective remission subsequent to a previous oophorectomy, one has the best chance of thereby inducing a second remission. In many clinics, the lesser operative morbidity consequent to hypophysectomy, the necessity for only a single operation, and the greater ease and safety of postoperative endocrine maintenance after the latter procedure, have resulted in less frequent utilization of adrenalectomy in favor of hypophysectomy. In our clinic, we have not as yet been convinced by clinical or analytical evidence of any superiority of adrenalectomy over and above therapy with adrenal corticoids, provided that oophorectomy has previously been carried out in patients under 65, and have not recommended it to our patients.

HYPOPHYSECTOMY.—Total hypophysectomy was introduced by Luft and Olivecrona as a palliative procedure for advanced mammary cancer in 1953, and this procedure was particularly studied by Pearson and associates in the United States. Remissions occur with frequency comparable to adrenalectomy or corticoid therapy; the highest frequency of objective remission, approaching 70%, is seen in cases selected because of their excellent previous response to oophorectomy

TABLE 9.—CORRELATION BETWEEN CLINICAL RESULTS OF ABLATIVE SURGERY AND TOTAL ESTROGEN EXCRETION (BROWN METHOD) IN BREAST CANCER

		NORMAL PREMENOPAUSE FEMALE	BREAST CANCER PATIENTS						TOTAL
			Post-oophorectomy			Post-menopause	Post-adrenalectomy	Post-hypophysectomy	
			Premenopause	Menses within 1 year	Postmenopause				
Mean total estrogen (estrone, estradiol and estriol) ± S.D.		15 mcg./24 hrs.	5.3 ±2.6	6.1 ±6.4	6.3 ±2.7	5.0 ±2.6	1.9 (not detected in 6 pts.)	3.4† (not detected in 8 pts.)	
No. analyses			230	50	31	81	123	295	810
No. patients			24	6	6	16	13	27	
Pts. without clinical remission	Estrogen excretion unchanged or increased			2	4*		2	4	12
	Estrogen excretion more than 50% decreased		2				2	1 (male breast)	5
Pts. with clinical remission	Estrogen secretion unchanged or increased							2	2
	Estrogen excretion more than 50% decreased		2	2			2	7	15
	Estrogen secretion absent throughout							2	

*Transient increase in estrogens after oophorectomy in 2–3 cases probably due to postoperative effects on adrenal cortex.
†Excluding 1 patient who excreted 51.6 mcg./24 hrs (4).

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(28). The operation itself is a far less formidable procedure than adrenalectomy, but is contraindicated in patients with extensive cerebral or pulmonary metastases, who may not tolerate anesthesia or craniotomy well. Usually, the patient is alert a few hours after the operation, and may be ambulatory in a few days.

Postoperatively, diabetes insipidus may be seen initially for a day or two in many patients; it then subsides, but returns on the 7th–10th day in 30–50%. This can be managed either by pitressin injections, or by nasal insufflation of the hormone. After a few days, 50 mg. of cortisone acetate provides adequate replacement therapy. When signs of hypothyroidism develop in patients with sufficient pituitary or infundibular damage, 60–120 mg. of desiccated thyroid should be added to the maintenance therapy. Hypophysectomized patients on cortisone and thyroid maintenance therapy seldom develop hyponatremia, collapse or other manifestations of adrenocortical insufficiency during intercurrent infections or trauma, but may become excessively sleepy and feeble during severe stress. It is usually wise to augment the dosage of cortisone, to 100–200 mg. daily under these circumstances.

There appears as yet little correlation between completeness of pituitary ablation, as determined by serial section of the sella turcica postmortem, and objective remissions induced by the operation. Transection of the stalk of the pituitary above the diaphragma sellae, which induces necrosis by interference with blood supply and interrupts the hypophysial portal system, also results in palliation for some patients. Patients under 60 appear to have the best clinical results from hypophysectomy. In our clinic, we offer hypophysectomy to patients under 45 with mammary cancer, in whom remissions induced by any steroid are likely to be brief, in the following circumstances: (a) after objective remission or arrest of disease has been induced by oophorectomy and adrenal corticoid therapy, when cancer reactivation is occurring or (b) inflammatory carcinoma of the breast.

The average remission following hypophysectomy is reported to last up to 12–15 months, with less than 5% surgical morbidity and 6–7% 30-day postoperative deaths (29). The highest remission rates have been reported by Luft and Olivecrona, Kennedy, Pearson, Ray and their associates, who perform hypophysectomy relatively early in metastatic breast carcinoma in highly selected cases. Other clinics have not

always been as successful in obtaining as frequent or as prolonged remissions, for a number of reasons, including the technical skill of the neurosurgeons, criteria used in case selection and the stage metastatic disease has reached when hypophysectomy is recommended (30). Thus far, we have seen only transient subjective benefit achieved by hypophysectomy performed for the indications listed above, in admittedly far-advanced patients. We have also noted that occasional patients relapsing from hypophysectomy will benefit subjectively if the maintenance dosage of cortisone or prednisone is increased to the amounts we have recommended for therapeutic use of adrenal corticoids.

The elegant clinical and endocrine studies of Bulbrook, Greenwood, Hadfield and Scowen of the Imperial Cancer Research Fund group and St. Bartholomew's Hospital in London have shown that hypophysectomy is the most effective ablative procedure in reducing urinary estrone, estradiol and estriol excretion (4). Their work also provides the first really good statistical evidence of a correlation between clinical remission following ablative procedures, and reduction induced in estrogen secretion (Table 9).

RADIATION THERAPY

In prostate cancer, the control of metastases should first be attempted through the relatively simple and initially highly effective procedures of hormonal therapy. Since most osseous metastases are osteoblastic, pathologic fractures are far less frequent than in mammary carcinomatosis, and local x-ray therapy is more often required for the relief of pain rather than for preservation of bone structure. Local x-ray therapy may be indicated over the nerve root distribution of segmental pain even in the absence of demonstrable osseous metastases, to reduce pain associated with perineural spread of tumor. In most patients, the location of painful areas is such that 250 kv. irradiation is adequate for palliation.

Local x-radiation in contrast is the first palliative procedure which should be utilized for the control of regional or distant metastases of mammary carcinoma. As long as local control of metastases can be achieved in this manner, we favor a conservative policy delaying any hormonal therapy until such time as multiple distant metastases are observed to be sympto-

matic, at which time we would favor starting the sequence of hormonal therapy with oophorectomy for those under 65, or treatment with sex hormones in those over 65. X-ray therapy is most valuable as an adjunct to hormonal therapy for ambulatory rehabilitation of patients with advanced disease, and in the prevention of pathologic fractures resulting from uncontrolled osteolytic lesions. When too many areas require x-ray therapy, we then turn to the alkylating chemotherapeutic agents because of their radiomimetic effects.

Although controlled scientific evidence is lacking, radiation therapy appears to be more effective in individual patients when the endocrine stimulus to tumor growth has been partly controlled, than in patients who have received no hormonal therapy. Furthermore, cortisone and prednisone through their anti-inflammatory action tend to reduce local vascular congestion and leukocytic reaction to metastases, with probable normalization of blood flow in their vicinity, as has been demonstrated by the studies of Lutz and Fulton in hamster cheek pouch tumor transplants. The cytotoxicity of ionizing radiation is greatly enhanced by the maintenance of high oxygen tension in the irradiated field, so that this anti-inflammatory action of adrenal corticoids may render metastases radiosensitive, which on previous radiotherapy appeared relatively insensitive.

Intracavitary radiation therapy with the use of radioactive agents and local infiltration of various radioactive agents is still in the investigative stage. As yet, there has been no convincing demonstration of the superiority of any of these highly specialized technics over the more generally available methods of x-radiation and chemotherapy utilizing radiomimetic agents.

CHEMOTHERAPY

The use of cytotoxic chemotherapy may materially assist in palliation of patients relapsing during hormonal therapy. The following agents have demonstrated objective cancerostatic activity, chiefly in patients with breast cancer:

MUSTARGEN.—Intravenously administered nitrogen mustards are initially largely taken up by pulmonary tissues and may be quite helpful in controlling pulmonary metastases. Since the lung parenchyma is quite sensitive to ionizing radia-

tions which may lead to subsequent pulmonary fibrosis, we prefer to utilize Mustargen as much as possible for the arrest of widespread pulmonary metastatic involvement. When there has been only slight previous bone marrow x-irradiation and the white count and platelet count are within normal limits, we administer 0.2 mg./kg. intravenously at 48-hour intervals for 3 doses; the last dose is omitted if leukopenia or thrombocytopenia appear imminent, or when there has been extensive bone marrow damage by metastatic cancer or irradiation. At least 6 weeks should elapse before repetition of therapy, with more cautious dosage on subsequent occasions. Mustargen is also useful administered locally into pleural or peritoneal effusions for their control, in 0.2–0.4 mg./kg. doses after withdrawal of most of the effusion, with care to avoid local cutaneous infiltration, or pocketing of the agent in a small localized area. Intravenous Mustargen therapy may also be helpful in immediate inhibition of cerebral and hepatic metastases. If response occurs, the clinician may be encouraged to proceed with local x-irradiation which is usually necessary if one is to maintain any regression of cancer metastases in these sites. Triethylene thiophosphoramide therapy in 5 intravenous daily doses of 0.2 mg./kg. each has not appeared to have any superiority in its spectrum of anticancer action over Mustargen other than the fact that it is nonirritating when administered into tissues directly. The antibreast cancer action reported by one investigator for this compound was probably considerably enhanced by the 50 mg. daily cortisone dosage simultaneously administered.

TRIETHYLENE MELAMINE.—This agent is most useful for treatment of ambulatory outpatients since it is administered orally and lacks most of the nausea and vomiting that Mustargen induces. It must be used with caution, however, since there is a fivefold variation in hematologic tolerance to the drug, some patients manifesting leukopenia or thrombocytopenia after as little as 5 mg. per week, and others tolerating as much as 25 mg. weekly initially. We have had no adverse results thus far starting therapy with 2.5 mg. weekly if bone marrow damage appears likely from the history, or with 5–10 mg. weekly in patients without osseous metastases and no recent x-ray therapy. The peripheral leukocyte count, differential and platelet estimation from the smear, are repeated each week before the next therapeutic dose, with no more than 40 mg. of drug being given during the first month of treat-

ment. The weekly dose that is tolerated by the marrow may be continued until a tumor effect is observed. It is taken on an empty stomach, with 15 cc. Maalox or other nonabsorbable antacid.

SUMMARY

Practicing physicians must never forget that the early diagnosis of these accessible cancers has more than a 50% chance of cure by surgery, which offers far greater benefits to the patient than any form of palliative treatment. The physicians' responsibility for early detection of these cancers necessitates education of their patients to demand a higher standard of preventive medical health care, so that they will co-operate by monthly breast self-examination or annual rectal (prostate) examinations. Hope for further improvements in palliative therapy increases as the numbers of hormonal derivatives and cytotoxic chemotherapeutic agents submitted to clinical trials in treatment of advanced cancers are multiplied. All types of palliation thus far discovered have severe limitations as a result of the adaptability of malignant neoplasms, so that medical treatment of either of these tumors is no substitute for adequate surgical therapy whenever possible.

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